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Brief Report

Dynamic Epidermal Cooling in Conjunction With Laser-Induced Photothermolysis of Port Wine Stain Blood Vessels

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When a cryogen spurt is applied to the skin surface for an appropriately short period of time (on the order of tens of milliseconds), the spatial distribution of cooling remains localized in the normal overlying epidermis, while leaving the temperature of the deeper port wine stain (PWS) blood vessels unchanged. Furthermore, cooling continues after pulsed laser exposure as cryogen remaining on the surface evaporates and removes heat deposited by light absorption in epidermal melanin. An additional advantage of dynamic cooling is a reduction in the level of pain and discomfort associated with flashlamp-pumped pulsed dye laser therapy of PWS. Preliminary clinical studies and supporting theoretical calculations demonstrate the feasibility of selective epidermal cooling while achieving photothermolysis of blood vessels during pulsed laser treatment of PWS.

Key words: cryogen, dermatology, port wine stain

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INTRODUCTION

The clinical objective in the treatment of a port wine stain (PWS) patient undergoing laser therapy is to maximize thermal damage to the PWS while at the same time minimizing nonspecific injury to the normal overlying epidermis [1–7]. One approach to achieve this objective is to cool selectively the most superficial layer of the skin. However, while a few techniques have been tried (e.g., application of ice cubes), none has proven entirely satisfactory [8–10] nor, most importantly, led to an improved therapeutic response (i.e., improved blanching of the PWS). All previously tried methods have failed due to the thermal response of skin to prolonged cooling when a near-linear steady-state temperature distribution is established from the surface down through the deeper skin layers. Therefore, in addition to cooling the epidermis, sustained cooling *also* reduces the core temperature of the PWS blood vessels. Any increase in the threshold for epidermal damage achieved by sustained cooling is almost entirely offset by the additional energy required to heat the PWS blood vessels for photothermolysis to occur.

With "dynamic" cooling, the epidermis can be cooled selectively [11,12]. When a cryogen spurt is applied to the skin surface for an appropriately short period of time (on the order of tens of milliseconds), the spatial distribution of cooling remains localized in the epidermis, while leaving the temperature of the deeper PWS vessels unchanged. We present preliminary clinical studies and supporting theoretical calculations that demonstrate the feasibility of selective epidermal cooling while achieving photothermolysis of blood vessels during pulsed laser treatment of PWS.

MATERIALS AND METHODS

We have developed a new methodology that allows for transient cooling of skin during pulsed laser PWS therapy [11,12]. Our method utilizes a test cryogen-tetrafluoroethane ($C_2H_2F_4$; boiling point (BP) = −26.2°C; an environmentally compatible, nontoxic, nonflammable freon substitute [13]) as a surface cooling agent. Short (tens of milliseconds) cryogen spurts are delivered onto the

skin surface through an electronically controlled solenoid valve. The cryogen spurt duration and the time interval between the application of the cryogen spurt and the onset of laser exposure are controlled by a digital delay generator. The cryogen released from the solenoid valve consists of droplets cooled by evaporation and mist formed by adiabatic expansion of vapor. On the surface of the skin, the cryogen is made to cover a nearly circular zone coincident with the laser spot.

Subjects (n = 14) are recruited for an ongoing evaluation from an on-site population of previously laser-treated or previously untreated PWS patients at the Beckman Laser Institute and Medical Clinic, University of California, Irvine. Permission to conduct an experimental protocol was sought and obtained from the Human Subjects Review Committee—Medical IRB (Institutional Review Board) of the University of California, Irvine. Port wine stain test sites are selected and identified by a skin marker. Test sites are selected on sectors of the PWS that are representative of the entire lesion. The sites selected for laser exposure without dynamic cooling are irradiated using the Candela (Wayland, MA) model SPTL-1 flashlamp-pumped pulsed dye laser (λ = 585 nm; t_p = 450 μs) using light dosages of 6–10 J/cm^2. The other test sites receive identical laser irradiation following exposure to a short (10–40 ms) cryogen spurt. At each light dosage, the effect of overlapping laser exposures (overlap pattern of 20% of the beam diameter) was compared with a single exposure. Test sites are observed for 6 months to determine if adverse effects occur and if clinically equivalent, significant blanching subsequently develops. Untreated areas of the PWS serve as controls (no light exposure).

RESULTS

The essential findings from all subjects' (n = 14) test sites, uncooled and cooled by 10–40 ms cryogen spurt durations, prior to flashlamp-pumped pulsed dye laser exposure (6–10 J/cm^2), may be summarized as follows. Post-irradiation observation of the uncooled sites at 2 days (Fig. 1A) following laser exposure reveals eschar formation indicative of epidermal necrosis using the highest light dosages (8–10 J/cm^2) delivered as single exposures or as successive overlapping pulses. Six months after laser exposure, adverse effects, such as hypertrophic scarring, changes in the normal skin pigmentation, atrophy, or induration, occurred on 10%, 25%, and 60% of the uncooled sites exposed to light dosages of 8, 9, and 10 J/cm^2, respectively. In contrast, post-irradiation observation reveals no skin surface textural changes on any of the cooled sites. Six months after laser exposure (Fig. 1B), the occurrence of clinically equivalent, significant blanching on all cooled test sites implies that a critical core temperature necessary to destroy the PWS blood vessels was achieved and sustained for a sufficient time with laser treatment. Furthermore, protection of the epidermis from thermal injury, produced by melanin light absorption at clinically relevant wavelengths, can be achieved effectively.

An additional advantage of dynamic cooling is a reduction in the level of pain and discomfort associated with flashlamp-pumped pulsed dye laser therapy. When the skin surface is cooled with 30–40 ms cryogen spurts (depending on the anatomical site) immediately prior to laser exposure, subjects report feeling "nothing at all." Subjects treated with cryogen spurts as short as 10 ms report significant improvement in the level of such discomfort.

DISCUSSION

During dynamic cooling, skin temperature is reduced as a result of supplying the heat of vaporization to the liquid cryogen droplets that strike the skin surface. As the skin temperature approaches the boiling point of the cryogen, the thermal energy supplied by the skin is no longer sufficient to vaporize the impinging cryogen droplets. At this stage, the droplets begin to accumulate on the skin surface, creating a layer consisting of liquid cryogen and ice (due to condensation of water vapor present in the surrounding air); the temperature of the layer is determined by the relative quantities of cryogen and ice. The cold front propagates into skin as a dispersive wave, and the time (t) required to reach a given depth (z) is proportional to the squared distance from the surface ($t \cong z^2/4\chi$, where χ is the thermal diffusivity (1.1×10^{-7} m^2/s) of human skin [14]).

Ideally, the duration of the cryogen spurt should be determined individually for each patient based on knowledge of the PWS vessel depth distribution [15–18]. Histopathology of the PWS example presented in Figure 1 determined that the blood vessels were located at a depth of 250–750 μm. The time delay before the cold front produced by dynamic cooling reaches the most superficial layer (250 μm) of PWS blood vessels is on the order of 100 ms. Therefore, cryogen spurt dura-

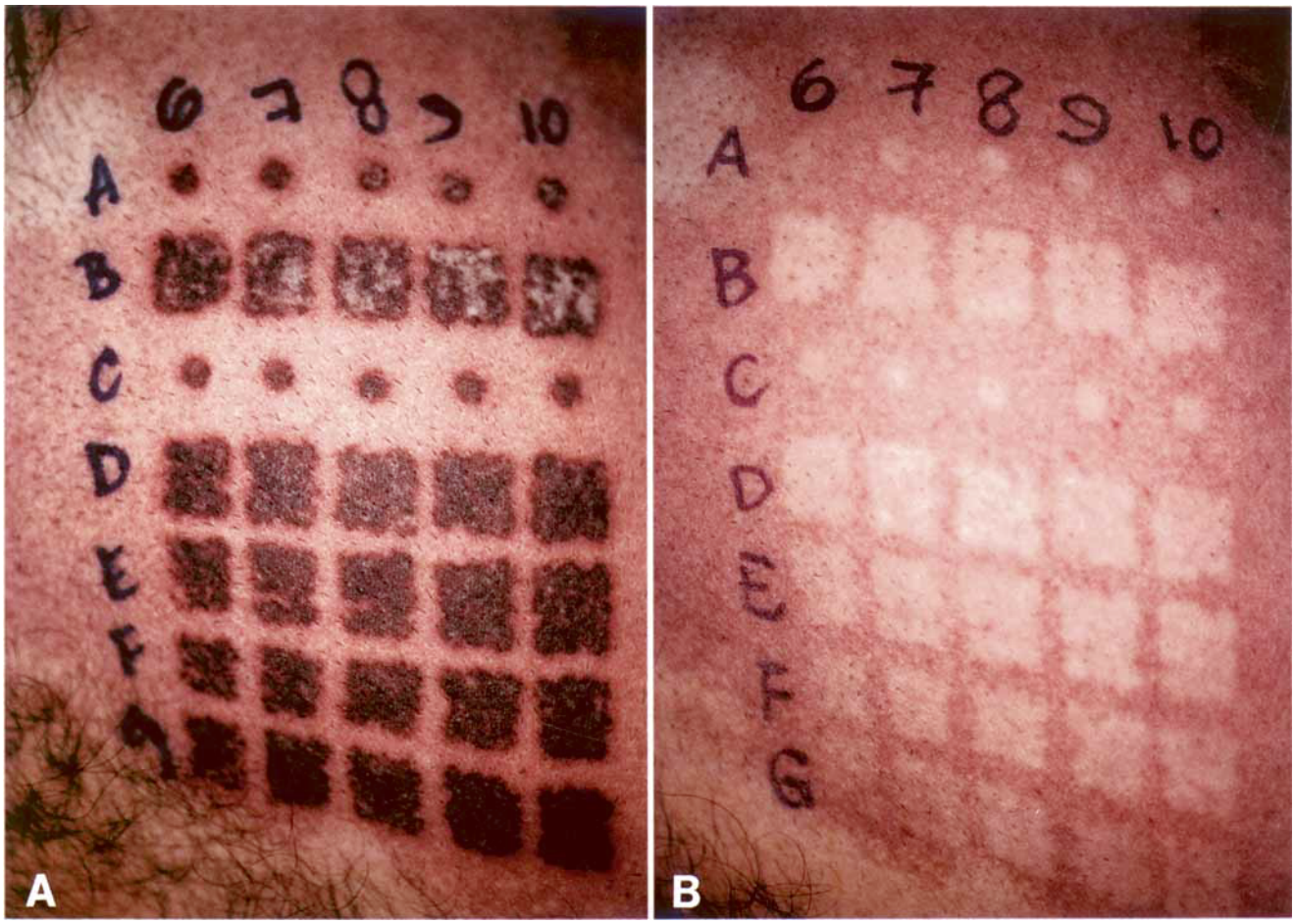

Fig. 1. **A:** Uncooled [*A* (single exposure), *B* (overlapped exposures)] and cooled [*C,D* (10 ms); *E* (20 ms); *F* (30 ms); and *G* (40 ms)] PWS test sites 2 days after laser exposure. Note eschar formation indicative of epidermal necrosis using the highest light dosages (8–10 J/cm^2) delivered as single exposures or as successive overlapping exposures. **B:** Uncooled [*A* (single exposure), *B* (overlapped exposures)] and cooled [*C,D* (10 ms); *E* (20 ms); *F* (30 ms); and *G* (40 ms)] PWS test sites 6 months after laser exposure. The presence of clinically equivalent, significant blanching on all cooled sites indicates laser photothermolysis of PWS blood vessels did occur.

tions of less than 40 ms were expected, and subsequently proven, to permit laser induced selective photothermolysis of PWS blood vessels.

Inasmuch as a detailed analysis of the thermodynamics at the cryogen-skin interface is too complex to present here, we assume the following (Fig. 2): (1) the existence of a liquid cryogen–ice layer that remains at a constant temperature throughout the cryogen spurt duration, which begins at time t = 0; (2) the presence of an infinitesimally thin layer positioned at $\chi = 0$, which acts as a thermal diffusion barrier between the liquid cryogen–ice layer and skin, creating a temperature discontinuity at the boundary ($\chi = 0$); (3) thermal energy transfer through the barrier is determined by the heat transfer coefficient, h (W/m^{2}K), which is assumed to be constant throughout the cryogen spurt duration. Given these assumptions, the heat flux (j_n) through the barrier is expressed as

$$j_n = h(\Delta T_0 - \Delta T_{x=0+}) = -\kappa \frac{\partial(\Delta T)}{\partial x}\Big|_{x=0+} \quad (1)$$

where κ is the thermal conductivity of skin (0.45 W/mK [14]), ΔT_0 is the difference between the liquid cryogen–ice layer and ambient skin temperature, and $\Delta T_{x=0+}$ is the difference between the skin surface and ambient temperature, which

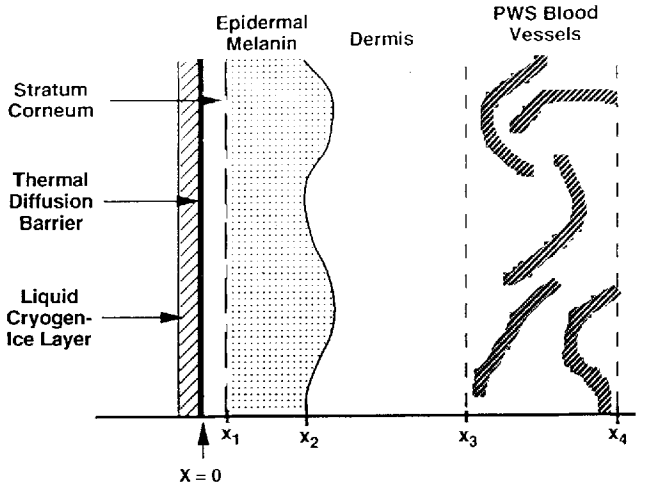

Fig. 2. Skin geometry assumed for dynamic cooling during pulsed laser treatment of PWS.

varies with time. Positive distances (x) are measured into the skin.

Due to melanin and hemoglobin laser light absorption, we assume temperature increases at time $\tau[\Delta T_L(t = \tau,\xi)$; *immediately after pulsed laser exposure*] are confined to the epidermis ($\Delta T_{o,E}$) and PWS ($\Delta T_{o,PWS}$),

$$\Delta T_L(t = \tau,\xi) = \begin{cases} \Delta T_{o,E}, x_1<\xi<x_2 \\ \Delta T_{o,PWS} \exp[-\mu(\xi-x_3)], x_3<\xi<x_4. \\ 0, \textit{all other } \xi \end{cases} \quad (2)$$

For the given temperature distribution (Eq. 2), the heat conduction equation [19] can be solved as follows:

$$\Delta T(t>\tau,x) = \Delta T_C(t,x) + \Delta T_E(t,x) + \Delta T_{PWS}(t,x), \quad (3)$$

where $\Delta T_C(t,x)$, $\Delta T_E(t,x)$ and $\Delta T_{PWS}(t,x)$ represent the evolution of the skin temperature change due to cooling, and, respectively, epidermal melanin and PWS heating at time t and distance x. Explicit expressions for each term are

$$\Delta T_C(t>0) = \Delta T_{o,C}\{erfc(\tilde{x} - \exp(2\tilde{h}\tilde{x} + \tilde{h}^2)erfc(\tilde{h} + \tilde{x})\}, \quad (3a)$$

where $\Delta T_{o,C} < 0$ represents the difference between the temperature of ambient skin and the cryogen-ice layer:

$$\Delta T_E(t>\tau) = \Delta T_{o,E}\left\{\frac{1}{2}[erf(\tilde{X}_j - \tilde{X}) - erf(\tilde{X}_j + \tilde{X})] - \exp[\tilde{H}^2 + 2\tilde{H}(\tilde{X}_j + \tilde{X})]erfc(\tilde{H} + \tilde{X}_j + \tilde{X})\right\}_{\tilde{X}_j=\tilde{X}_1}^{\tilde{X}_j=\tilde{X}_2} \quad (3b)$$

$$\Delta T_{PWS}(t > \tau) = \Delta T_{o,PWS} \exp(2\tilde{K}\tilde{X}_3)$$

$$\left\{\frac{1}{2}\exp(\tilde{K}^2)\left[\exp(-2\tilde{K}\tilde{X})erf(\tilde{X}_j - \tilde{X} + \tilde{K}) + \frac{\tilde{K}+\tilde{H}}{\tilde{K}-\tilde{H}}\exp(2\tilde{K}\tilde{X})erf(\tilde{X}_j + \tilde{X} + \tilde{K})\right] + \frac{\tilde{H}}{\tilde{K}-\tilde{H}}\exp[\tilde{H}^2 + 2\tilde{H}\tilde{X} + 2(\tilde{H}-\tilde{K})\tilde{X}_j]erfc(\tilde{H} + \tilde{X}_j + \tilde{X})\right\}_{\tilde{X}_j=\tilde{X}_3}^{\tilde{X}_j=\tilde{X}_4} \quad (3c)$$

where $\tilde{x} = x/2\sqrt{\chi t}$, $\tilde{X}_i = x_i/2\sqrt{\chi(t-\tau)}$, and i = 1, 2, 3, or 4, $\tilde{h} = h\sqrt{\chi t}/\kappa$, $\tilde{H} = h\sqrt{\chi(t-\tau)}/\kappa$, and $\tilde{K} = \mu\sqrt{\chi(t-\tau)}$. $\}_{\tilde{X}_j=\tilde{X}_1}^{\tilde{X}_j=\tilde{X}_2}$ denotes that the expressions within the bracket are evaluated at $\tilde{X}_j = \tilde{X}_2$ and $\tilde{X}_j = \tilde{X}_1$; the result at the lower limit is then subtracted from the result at the upper limit as in the evaluation of a definite integral. Note: $\tilde{K}$ does not become close to $\tilde{H}$ since $\tilde{K}$ is always greater than $\tilde{H}$ by the factor $h/k\mu$ ($\approx$27 for h = 40,000 W/m^{2}K, k = 0.45 W/mK, and μ = 3,300 m^{-1}).

The spatial temperature distributions in skin for PWS blood vessels located at a depth of x_3 = 250 μm to x_4 = 750 μm (identical to the PWS example presented in Fig. 1), uncooled and cooled by a 40 ms cryogen spurt, are illustrated in Figure 3A and 3B, respectively. It is assumed (1) epidermal melanin heating ($\Delta T_{o,E}$ = 60°C) occurs over a depth of x_1 = 10 μm to x_2 = 50 μm; (2) PWS heating ($\Delta T_{o,PWS}$ = 60°C) is attenuated (μ^{-1} = 300 μm) with depth corresponding to blood vessels occupying a 10% fractional volume of the total dermis and an absorption of whole blood = 33,000 m^{-1}; (3) cooling continues after pulsed laser exposure as cryogen remaining on the surface evaporates and removes heat deposited by light absorption in epidermal melanin; (4) the temperature of the liquid cryogen–ice layer on the skin surface is −10°C ($\Delta T_{o,C}$ = −40°C) [20]; and (5) the heat transfer coefficient, h, is equal to 40,000 W/m^{2}K [20].

As illustrated in Figure 3, the maximum surface temperature achieved immediately after laser exposure is lower on the cooled example as compared with the uncooled example (in some cases by as much as 40°C [12]). Cryogen remaining on the skin evaporates and continues to re-

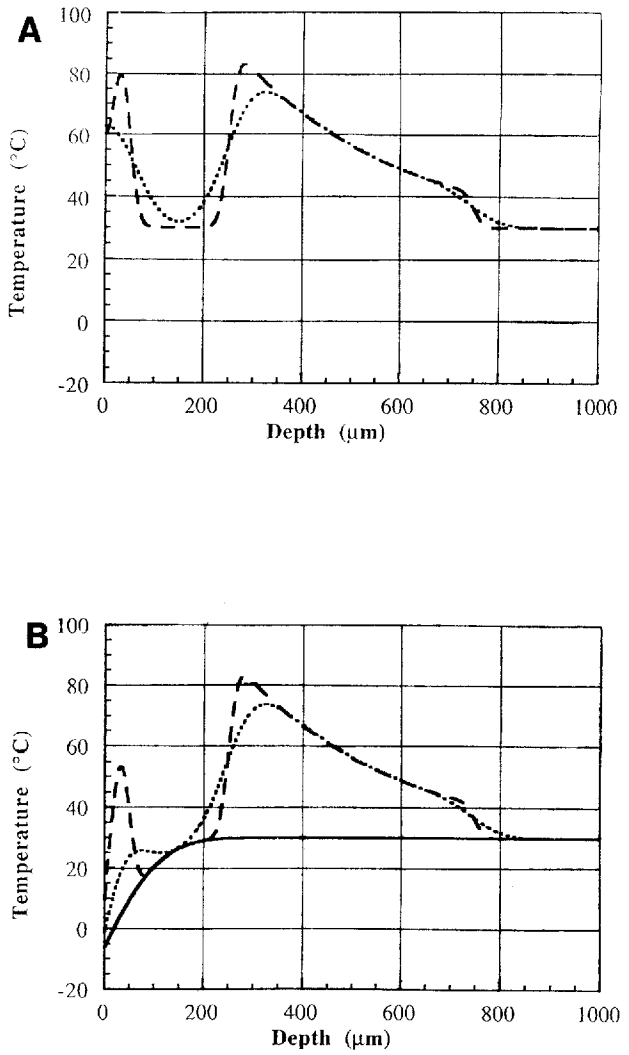

Fig. 3. **A:** Spatial temperature distribution in uncooled skin vs. depth for PWS blood vessels located at a depth of 250–750 μm. Curves show temperature distribution at 1 ms (_ _ _) and 10 ms (. . . .) after pulsed laser exposure. **B:** Spatial temperature distribution in cooled skin (40 ms before the laser pulse) vs. depth for PWS blood vessels located at a depth of 250–750 μm. Curves show temperature distribution immediately after the cryogen spurt (_____) and at 1 ms (_ _ _), and 10 ms (. . . .) after pulsed laser exposure. Although the temperature in the most superficial skin layer (stratum corneum) will be reduced from 30°C to −10°C, the spatial distribution of cooling remains localized in the epidermis while the temperature of the deeper PWS blood vessels located at a depth of 250–750 μm remains unchanged when compared with the uncooled example.

move residual heat following laser irradiation. Therefore, the temperature of the post-irradiated epidermis decreases more rapidly on the cooled example as compared with an uncooled example. Although the temperature in the most superficial skin layer (stratum corneum) will be reduced from 30°C to −10°C because the cryogen spurt duration is only 40 ms, the spatial distribution of cooling remains localized in the epidermis, while the temperature of the deeper PWS blood vessels located at a depth of 250–750 μm remains unchanged when compared with the uncooled example.

In conclusion, preliminary clinical studies and supporting theoretical calculations demonstrate the feasibility of selective epidermal cooling while achieving photothermolysis of blood vessels during pulsed laser treatment of PWS. However, several key technical issues need to be addressed in regards to the development of the cooling apparatus: (1) distance between the valve and the skin surface; (2) boiling point of the cryogen; (3) velocity of the cryogen before striking the skin surface; (4) quantity of cryogen deposited on the skin surface; and (5) orientation of the valve with respect to the skin surface. Studies are currently underway in our laboratory to determine the physical limits of dynamic cooling during pulsed laser treatment of PWS and other clinical entities [e.g., tattoos and dermal melanocytic lesions (nevus of Ota)].

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